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(54) Title: PHARMACEUTICAL PRODUCTS AND COMPOSITIONS COMPRISING SPECIFIC ANTICHOLINERGIC AGENTS, BETA-2 AGONISTS AND CORTICOSTEROIDS

(57) Abstract: This invention relates to pharmaceutical products and compositions for use in the treatment of asthma and related disorders, and especially but not exclusively for the treatment of chronic obstructive pulmonary disease (COPD). More particularly, the invention provides pharmaceutical products and compositions comprising specific anticholinergic agents, β-2 agonists and corticosteroids.

PHARMACEUTICAL PRODUCTS AND COMPOSITIONS COMPRISING SPECIFIC ANTICHOLINERGIC AGENTS, BETA-2 AGONISTS AND CORTICOSTEROIDS

This invention relates to pharmaceutical products and compositions for use in the treatment of asthma and related disorders, and especially but not exclusively for the treatment of chronic obstructive pulmonary disease (COPD).

The pathophysiology of asthma and related disorders involves various distinct symptoms, including bronchoconstriction, inflammation of the airways, and increased mucous secretion, which results in wheezing, coughing and shortness of breath. A persistent or recurrent cough may exacerbate the problem by causing further irritation and inflammation of the airways. The causes of asthma are wide-ranging and not yet fully understood.

Bronchoconstriction occurs due to bronchial smooth muscle spasm and airway inflammation with mucosal edema. Asthma and other related disorders, have been known to be treated with β-2 adrenergic receptor agonists (β-2 agonist) as they provide a bronchodilator effect to the patients, resulting in relief from the symptoms of breathlessness. β-2 Agonists can be short acting for immediate relief, or long acting for long-term prevention, of asthma symptoms. Short acting β-2 agonists currently available include: salbutamol, biltolterol, pirbuterol and terbutaline. Long acting β-2 agonists currently available include salmeterol and formoterol.

Whilst it is also known that β-2 agonists provide symptomatic relief of bronchoconstriction in patients, another component of asthma, i.e. inflammation, often requires separate treatment. Typically this involves treatment with a steroid. Indeed, treatment with a corticosteroid is considered one of the most potent and effective therapies currently available for persistent asthma. Currently available corticosteroids include: beclomethasone, budesonide, flunisolide, fluticasone, mometasone and triamcinolone.

Bronchoconstriction and inflammation are also associated with bronchial plugging with secretions, which may be treated with anti-cholinergic agents, such as troventol, ipratropium, oxitropium and tiotropium.

These medicaments can be administered in different ways, such as in MDIs (metered-dosage inhalers), in DPIs (dry powder inhalers), and in oral and liquid formulations. Treatment in these different ways calls for the patient to comply with different dosage regimens, different frequencies of administration, etc. Also, since most of the medications are

in the form of aerosols, the patient is required to carry several formulations and dispensers, one for each of these medicaments.

To assist patient compliance, combination products are known, e.g. an inhalation combination medication of fluticasone propionate and salmeterol, the combination being provided in one easy-to-use device. This combination product provides simultaneous treatment of airway constriction by means of the β-2 agonist (salmeterol), and treatment of inflammation by means of the steroid (fluticasone propionate).

A combination of ipratropium bromide and salbutamol is also known. This combination therapy provides an anti-cholinergic (ipratropium bromide) to reduce the bronchial secretions and a β-2 agonist (salbutamol) to reduce constriction. Other described combinations include ipratropium and salbutamol (WO 01/76601) and tiotropium and formoterol (WO 00/47200).

It would be highly desirable, however, to provide a combination therapy suitable to reduce bronchial inflammation, bronchial constriction and bronchial secretions in a single product or dosage form. It would also be desirable to provide such a combination product or composition in a form whereby the correct dosage of the various components is easily and safely administered.

We have now found that certain therapeutic three-in-one combinations comprising specific β-2 agonists, anti-cholinergics and steroids surprisingly provide an enhanced, synergistic, effect in terms of treatment of bronchoconstriction, inflammation and mucous secretions of airways. Also the three-in-one combination therapy as provided by the present invention is an extremely patient-friendly combination, which results in maximum patient compliance and better control of asthma than the known combinations or single therapies.

The present invention further provides, therefore, a pharmaceutical product comprising any one of the following combinations of therapeutic agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more of the therapeutic agents is indicated:

(i) salmeterol, ciclesonide and tiotropium;

(ii) formoterol, budesonide and ipratropium;

(iii) formoterol, ciclesonide and tiotropium;

(iv) formoterol, budesonide and oxitropium;

(v) salbutamol, beclomethasone and ipratropium;

(vi) salbutamol, budesonide and tiotropium;

(vii) terbutaline, fluticasone and tiotropium;

(viii) terbutaline, fluticasone and ipratropium;

(ix) salbutamol, budesonide and ipratropium;

(x) salmeterol, fluticasone and ipratropium;

(xi) salmeterol, budesonide and ipratropium;

(xii) salmeterol, fluticasone and tiotropium; and

(xiii) formoterol, budesonide and tiotropium.

It will also be appreciated from the above, that the respective therapeutic agents of the combined preparations can be administered simultaneously, either in the same or different pharmaceutical formulations, or separately or sequentially. If there is separate or sequential administration, it will also be appreciated that the subsequently administered therapeutic agents should be administered to a patient within a time scale so as to achieve, or more particularly optimise, the above referred to advantageous synergistic therapeutic effect of a combined preparation as present in a pharmaceutical product according to the present invention.

The present invention also provides a pharmaceutical composition comprising any one of the following combinations of therapeutic agents:

(i) salmeterol, ciclesonide and tiotropium;

(ii) formoterol, budesonide and ipratropium;

(iii) formoterol, ciclesonide and tiotropium;

(iv) formoterol, budesonide and oxitropium;

(v) salbutamol, beclomethasone and ipratropium;

(vi) salbutamol, budesonide and tiotropium;

(vii) terbutaline, fluticasone and tiotropium;

(viii) terbutaline, fluticasone and ipratropium;

(ix) salbutamol, budesonide and ipratropium;

(x) salmeterol, fluticasone and ipratropium;

(xi) salmeterol, budesonide and ipratropium;

(xii) salmeterol, fluticasone and tiotropium; and

(xiii) formoterol, budesonide and tiotropium.

together with a pharmaceutically acceptable carrier or excipient therefor.

The abovementioned compounds may exist, and be used in the present invention, in various active forms, whilst retaining the same physiological function. For example, the anticholinergic agents, β-2 agonists and corticosteroids may exist as various acid addition salts, such as those formed from hydrochloric, hydrobromic, sulphuric, acetic, lactic, maleic, tartaric, oxalic, methanesulphonic, p-toluenesulphonic and benzenesulphonic acids. The skilled person will also appreciate that the abovementioned compounds may also exist as esters and (R) and (S) enantiomers and provided the desired activity is maintained, they may be used in the present invention.

Specific triple combinations of the invention as illustrated by the Examples are:

(i) salmeterol, ciclesonide and tiotropium bromide;

(ii) formoterol, budesonide and ipratropium;

(iii) formoterol, ciclesonide and tiotropium bromide;

(iv) formoterol, budesonide and oxitropium;

(v) salbutamol sulphate, beclomethasone and ipratropium;

(vi) salbutamol sulphate, budesonide and tiotropium bromide;

(vii) terbutaline sulphate, fluticasone and tiotropium bromide;

(viii) terbutaline sulphate, fluticasone and ipratropium bromide;

(ix) salbutamol sulphate, budesonide and ipratropium bromide;

(x) salmeterol, fluticasone propionate and ipratropium bromide;

(xi) salmeterol, budesonide and ipratropium bromide;

(xii) salmeterol, fluticasone propionate and tiotropium bromide; and

(xiii) formoterol, budesonide and tiotropium bromide.

The pharmaceutical composition may be provided in any suitable dosage form. Preferably the composition is in the form of a suspension, a particulate suspension or a clear solution. The pharmaceutical composition of the present invention may alternatively be provided as an inhalation powder.

The pharmaceutical composition of the present invention may be administered by any suitable administration method and it may be preferred that the composition is administered as an aerosol. The composition of the present invention can comprise a propellant-containing dosage aerosol, an inhalation powder or a propellant free inhalation solution or suspension. The compositions of the present invention may thus be provided by, for example, a metered

dose inhaler (MDI), dry powder inhaler (DPI), nebules, nebuliser or nasal spray.

In the case of a propellant-containing dosage aerosol, typically the propellant can be selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoroethane, monofluorotrichloromethane and dichlorodifluoromethane.

In the case of a particulate suspension or a solution for the propellant-containing aerosol composition, the composition may further comprise one or more co-solvents. The composition may comprise both a propellant and a co-solvent, in which case it is desirable that the co-solvent has a greater polarity than the propellant. The co-solvent used may be any suitable solvent. Typically the co-solvent is ethanol. Generally the ratio of propellant to solvent is between 50:50 to 99:1.

If aerosolized, the formulation may consist of a surface-active agent to stabilize the formulation and for the lubrication of a valve system in the inhaler/nebuliser/nasal spray.

Some of the most commonly used surface-active agents in the aerosol formulations are oils derived from natural sources, such as corn oil, olive oil, cotton seed oil and sunflower seed oil and phospholipids. Preferred surfactants for use according to the present invention are oleic acid, lecithin or sorbitol trioleate. In these embodiments, the surface-active agents are preferably used in the formulations in the ratio of 0.00002 wt% wt to 20 wt% of the active ingredients. The surface-active agents may exceed this weight ratio in cases where drug concentration in the formulation is very low.

The active ingredients in all the above aerosol formulations are preferably in the concentration of 0.001 wt% to 5 wt% of the total formulation.

The active ingredients are provided in an appropriate particle size, generally in the range from nano-size to about 12 μm. Preferably, approximately 95% are below 5 or 6 μm (micrometers), with the all particles being below 12 μm (when measured by laser), or approximately 95% below 2.5 μm and the rest of the particles between 2.5-5 μm (when measured by microscope).

According to another aspect of the invention there is provided an aerosol device, comprising a housing containing a composition as described above, and a dispensing mechanism for dispensing the composition from the housing in a metered dose.

The dispensing mechanism may include a valve capable of releasing a metered dosage of the composition. Preferably the housing is sealed and pressurized at a pressure exceeding atmospheric pressure.

The housing may be metallic, preferably aluminum. Preferably, the housing is plastic-coated, lacquer-coated or anodised. The composition of the present invention may be placed in the housing through a suitable metering device.

Preferred combinations of active ingredients for administration by way of a propellant-containing dosage aerosols according to the present invention are further illustrated by the Examples and can include any one of the following combinations:

(i) salmeterol, ciclesonide and tiotropium;

(ii) formoterol, budesonide and ipratropium;

(iii) formoterol, ciclesonide and tiotropium;

(iv) formoterol, budesonide and oxitropium;

(v) salbutamol, beclomethasone and ipratropium;

(vi) salbutamol, budesonide and tiotropium;

(vii) terbutaline, fluticasone and tiotropium;

(viii) salmeterol, fluticasone and tiotropium; and

(ix) formoterol, budesonide and tiotropium.

More specifically the following may be administered by way of propellant-containing dosage aerosols according to the present invention:

(i) salmeterol, ciclesonide and tiotropium bromide;

(ii) formoterol, budesonide and ipratropium;

(iii) formoterol, ciclesonide and tiotropium bromide;

(iv) formoterol, budesonide and oxitropium;

(v) salbutamol sulphate, beclomethasone and ipratropium;

(vi) salbutamol sulphate, budesonide and tiotropium bromide;

(vii) terbutaline sulphate, fluticasone and tiotropium bromide;

(viii) salmeterol, fluticasone propionate and tiotropium bromide;

(ix) formoterol, budesonide and tiotropium bromide.

In the case where the triple combinations of the present invention are provided as inhalation powders, typically suitable pharmaceutically acceptable excipients may be selected from monosaccharides, disaccharides, oligosaccharides, polysaccharides or the like, with the use of lactose as the excipient in the inhalation powders of the present invention being preferred. The inhalation powders of the present invention can typically be administered by means of dry powder inhalers known in the art. Preferred combinations of active ingredients

for administration by way of inhalation powders according to the present invention are further illustrated by the Examples and can include any one of the following combinations:

(i) salmeterol, ciclesonide and tiotropium;

(ii) formoterol, budesonide and ipratropium;

(iii) formoterol, ciclesonide and tiotropium;

(iv) salbutamol, beclomethasone and ipratropium;

(v) salbutamol, budesonide and tiotropium; and

(vi) terbutaline, fluticasone and tiotropium.

More specifically the following may be administered by way of inhalation powders according to the present invention:

(i) salmeterol, ciclesonide and tiotropium bromide;

(ii) formoterol, budesonide and ipratropium;

(iii) formoterol, ciclesonide and tiotropium bromide;

(iv) salbutamol sulphate, beclomethasone and ipratropium;

(v) salbutamol sulphate, budesonide and tiotropium bromide; and

(vi) terbutaline sulphate, fluticasone and tiotropium bromide.

The propellant free inhalation solutions of the present invention are typically suitable for administration by way of nebulisation, employing nebulisers well known in the art that can advantageously be employed to produce inhalable aerosols comprising the triple combinations of active ingredients according to the present invention. Preferred combinations of active ingredients for administration by way of propellant free inhalation solutions according to the present invention are further illustrated by the Examples and can include any one of the following combinations:

(i) terbutaline, fluticasone and ipratropium;

(ii) salbutamol, budesonide and ipratropium;

(iii) salmeterol, fluticasone and ipratropium; and

(iv) salmeterol, budesonide and ipratropium.

More specifically the following may be administered by way of propellant free inhalation solutions according to the present invention:

(i) terbutaline sulphate, fluticasone and ipratropium bromide;

(ii) salbutamol sulphate, budesonide and ipratropium bromide;

(iii) salmeterol, fluticasone propionate and ipratropium bromide; and

(iv) salmeterol, budesonide and ipratropium bromide.

According to another aspect of the invention, there is provided the use of any one of the following combinations in the manufacture of a medicament for the prophylaxis or treatment of conditions for which administration of one or more of the therapeutic agents is indicated:

(i) salmeterol, ciclesonide and tiotropium;
(ii) formoterol, budesonide and ipratropium;
(iii) formoterol, ciclesonide and tiotropium;
(iv) formoterol, budesonide and oxitropium;
(v) salbutamol, beclomethasone and ipratropium;
(vi) salbutamol, budesonide and tiotropium;
(vii) terbutaline, fluticasone and tiotropium;
(viii) terbutaline, fluticasone and ipratropium;
(ix) salbutamol, budesonide and ipratropium;
(x) salmeterol, fluticasone and ipratropium;
(xi) salmeterol, budesonide and ipratropium;
(xii) salmeterol, fluticasone and tiotropium; and
(xiii) formoterol, budesonide and tiotropium.

The triple combinations as provided by the present invention are useful for the treatment of inflammatory or respiratory tract diseases, especially asthma and / or chronic obstructive pulmonary disease (COPD), by simultaneous or successive administration.

According to another aspect of the invention there is provided a method for the prophylaxis or treatment of inflammatory or respiratory tract diseases, said method comprising administering either sequentially or simultaneously, to a patient in need thereof, a therapeutically effective amount of any one of the following combinations:

(i) salmeterol, ciclesonide and tiotropium;
(ii) formoterol, budesonide and ipratropium;
(iii) formoterol, ciclesonide and tiotropium;
(iv) formoterol, budesonide and oxitropium;
(v) salbutamol, beclomethasone and ipratropium;
(vi) salbutamol, budesonide and tiotropium;
(vii) terbutaline, fluticasone and tiotropium;

(viii) terbutaline, fluticasone and ipratropium;

(ix) salbutamol, budesonide and ipratropium;

(x) salmeterol, fluticasone and ipratropium;

(xi) salmeterol, budesonide and ipratropium;

(xii) salmeterol, fluticasone and tiotropium; and

(xiii) formoterol, budesonide and tiotropium.

Any of the following specific triple combinations of the invention as illustrated by the Examples are suitable to be employed in the manufacture of a medicament, or a method of treatment, as referred to above:

(i) salmeterol, ciclesonide and tiotropium bromide;

(ii) formoterol, budesonide and ipratropium;

(iii) formoterol, ciclesonide and tiotropium bromide;

(iv) formoterol, budesonide and oxitropium;

(v) salbutamol sulphate, beclomethasone and ipratropium;

(vi) salbutamol sulphate, budesonide and tiotropium bromide;

(vii) terbutaline sulphate, fluticasone and tiotropium bromide;

(viii) terbutaline sulphate, fluticasone and ipratropium bromide;

(ix) salbutamol sulphate, budesonide and ipratropium bromide;

(x) salmeterol, fluticasone propionate and ipratropium bromide;

(xi) salmeterol, budesonide and ipratropium bromide;

(xii) salmeterol, fluticasone propionate and tiotropium bromide; and

(xiii) formoterol, budesonide and tiotropium bromide.

These products or compositions as provided by the present invention are especially useful in the treatment of COPD. They will normally be administered by inhalation, once or twice daily. By way of example, a preferred dosage for twice daily administrations would be:

a) formoterol (6 mcg)/budesonide (200 mcg)/ipratropium (40 mcg)

b) formoterol (6 mcg)/budesonide (200 mcg)/oxitropium (200 mcg).

The invention will now be described with reference to the following examples, which do not limit the scope of the invention in any way.

Example 1

	Per aerosol housing
Tiotropium bromide	2.4 mg
Salbutamol	24 mg
Budesonide	24 mg
1,1,1,2-Tetrafluoroethane	18.2 gms

Example 2

	Per aerosol housing
Tiotropium bromide	2.4 mg
Terbutaline Sulphate	60 mg
Fluticasone	12 mg
1,1,1,2-Tetrafluoroethane	18.2 gms

In the above formulations (Examples 1 and 2), the active ingredients were initially weighed in an aluminum can. Then a metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA 134a was charged through the metering valve.

Example 3

	Per aerosol housing
Tiotropium bromide	2.4 mg
Salbutamol	24 mg
Budesonide	24 mg
Ethanol	2.73 gms
1,1,1,2-Tetrafluoroethane	15.47 gms

In the above formulation the active ingredients were first weighed in an aluminum can, then the ethanol was added and the solution was sonicated for 5 min. The metering valve was placed on the can and crimped with a vacuum crimper, and then propellant HFA 134a was charged through the metering valve.

Example 4

	Per aerosol housing
Tiotropium bromide	2.4 mg
Salbutamol	24 mg
Budesonide	24 mg
Ethanol	2.73 gms
Oleic acid (10%)	5.04 mg
1,1,1,2-Tetrafluoroethane	15.47 gms

In the above formulation the active ingredients were first weighed in an aluminum can then the ethanol and the surfactant were added and solution was sonicated for 5 min. The metering valve was placed on the can and crimped with a vacuum crimper and then the HFA 134a was charged through the metering valve.

Example 5

	Per aerosol housing
Tiotropium bromide	2.4 mg
Terbutaline Sulphate	60 mg
Fluticasone	12 mg
Ethanol	0.364 gms
1,1,1,2-Tetrafluoroethane	18.2 gms

Example 6

	Per aerosol housing
Tiotropium bromide	2.4 mg
Terbutaline Sulphate	60 mg
Fluticasone	12 mg
Ethanol	0.364 gms
Oleic acid (0.02%)	0.014 mg
1,1,1,2-Tetrafluoroethane	17.83 gms

The above formulations (Examples 5 and 6) were weighed in an aluminum can, and a metering valve was crimped on the can and the propellant added.

Example 7

Ingredients	Quantity (Per aerosol housing)
Tiotropium bromide	1.8 mg
Salmeterol	5.81 mg
Ciclesonide	8.0 mg
1,1,1,2-Tetrafluoroethane	12.2 g

The active ingredients were initially weighed in an aluminum can. The metering valve was then placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 8

Ingredients	Quantity (Per aerosol housing)
Tiotropium bromide	1.8 mg
Salmeterol	5.81 mg
Ciclesonide	8.0 mg

Ethanol (2%)	0.244 g
1,1,1,2-Tetrafluoroethane	12 g

The active ingredients were initially weighed in an aluminum can, then ethanol was added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 9

Ingredients	Quantity (Per aerosol housing)
Tiotropium bromide	1.8 mg
Salmeterol	5.81 mg
Ciclesonide	8.0 mg
Ethanol (2%)	0.244 g
Oleic acid (0.02%)	0.003 mg
1,1,1,2-Tetrafluoroethane	12 g

The active ingredients were initially weighed in an aluminum can, then ethanol and oleic acid were added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 10

Ingredients	Quantity (Per aerosol housing)
Formoterol	1 mg
Ipratropium	3.2 mg
Budesonide	8.0 mg
1,1,1,2-Tetrafluoroethane	12.2 g

The active ingredients were initially weighed in an aluminum can. The metering valve was then placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 11

Ingredients	Quantity (Per aerosol housing)
Formoterol	1 mg
Ipratropium	3.2 mg
Budesonide	8.0 mg
Ethanol (15%)	1.83 g
1,1,1,2-Tetrafluoroethane	18.2 g

The active ingredients were initially weighed in an aluminum can, then ethanol was added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 12

Ingredients	Quantity (Per aerosol housing)
Formoterol	1.0 mg
Ipratropium	3.2 mg
Budesonide	8.0 mg
Ethanol	1.83 g
Lecithin (1%)	0.122 mg
1,1,1,2-Tetrafluoroethane	18.2 g

The active ingredients were initially weighed in an aluminum can, then ethanol and lecithin were added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 13

Ingredients	Quantity (Per aerosol housing)
Tiotropium Bromide	1.8 mg
Formoterol	1.0 mg
Ciclesonide	8.0 mg
1,1,1,2-Tetrafluoroethane	12.2 g

The active ingredients were initially weighed in an aluminum can. The metering valve was then placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 14

Ingredients	Quantity (Per aerosol housing)
Tiotropium Bromide	1.8 mg
Formoterol	1.0 mg
Ciclesonide	8.0 mg
Ethanol (15%)	1.83 g
1,1,1,2-Tetrafluoroethane	10.4 g

The active ingredients were initially weighed in an aluminum can, then ethanol was added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 15

Ingredients	Quantity (Per aerosol housing)
Tiotropium Bromide	1.8 mg

Formoterol	1.0 mg
Ciclesonide	8.0 mg
Ethanol	1.83 g
Lecithin (1%)	0.10 mg
1,1,1,2-Tetrafluoroethane	10.4 g

The active ingredients were initially weighed in an aluminum can, then ethanol and lecithin were added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 16

Ingredients	Quantity (Per aerosol housing)
Oxitropium	4.8 mg
Formoterol	1.0 mg
Budesonide	8.0 mg
1,1,1,2-Tetrafluoroethane	12.2 g

The active ingredients were initially weighed in an aluminum can. The metering valve was then placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 17

Ingredients	Quantity (Per aerosol housing)
Oxitropium	4.8 mg
Formoterol	1.0 mg
Budesonide	8.0 mg
Ethanol (15%)	1.83 g
1,1,1,2-Tetrafluoroethane	10.4 g

The active ingredients were initially weighed in an aluminum can, then ethanol was added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 18

Ingredients	Quantity (Per aerosol housing)
Oxitropium	4.8 mg
Formoterol	1.0 mg
Budesonide	8.0 mg
Ethanol (15%)	1.83 g
Lecithin (1%)	0.138 mg
1,1,1,2-Tetrafluoroethane	10.4 g

The active ingredients were initially weighed in an aluminum can, then ethanol and lecithin were added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 19

Ingredients	Quantity (Per aerosol housing)
Salbutamol sulphate	28.8 mg
Beclomethasone	12.0 mg
Ipratropium	4.8 mg
1,1,1,2-Tetrafluoroethane	18.2 g

The active ingredients were initially weighed in an aluminum can. The metering valve was then placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 20

Ingredients	Quantity (Per aerosol housing)
Salbutamol sulphate	28.8 mg
Beclomethasone	12.0 mg
Ipratropium	4.8 mg
Ethanol (2.5 %)	0.455 g
1,1,1,2-Tetrafluoroethane	17.75 g

The active ingredients were initially weighed in an aluminum can, then ethanol was added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 21

Ingredients	Quantity (Per aerosol housing)
Salbutamol sulphate	28.8 mg
Beclomethasone	12.0 mg
Ipratropium	4.8 mg
Ethanol (2.5 %)	0.455 g
Oleic acid (0.02%)	0.009mg
1,1,1,2-Tetrafluoroethane	17.75 g

The active ingredients were initially weighed in an aluminum can, then ethanol and oleic acid were added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 22

Ingredients	Quantity (Per aerosol housing)
Salbutamol sulphate	28.8 mg
Tiotropium bromide	2.7 mg
Budesonide	12 mg
1,1,1,2-Tetrafluoroethane	18.2 g

The active ingredients were initially weighed in an aluminum can. The metering valve was then placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 23

Ingredients	Quantity (Per aerosol housing)
Salbutamol sulphate	28.8 mg
Tiotropium bromide	2.7 mg
Budesonide	12 mg
Ethanol (2%)	0.364 g
1,1,1,2-Tetrafluoroethane	17.83 g

The active ingredients were initially weighed in an aluminum can, then ethanol was added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 24

Ingredients	Quantity (Per aerosol housing)
Salbutamol sulphate	28.8 mg
Tiotropium bromide	2.7 mg

Budesonide	12 mg
Ethanol (2%)	0.364 g
Oleic acid (0.02%)	0.0087 mg
1,1,1,2-Tetrafluoroethane	17.83 g

The active ingredients were initially weighed in an aluminum can, then ethanol and oleic acid were added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 25

Ingredients	Quantity (Per aerosol housing)
Terbutaline sulphate	40 mg
Tiotropium bromide	1.8 mg
Fluticasone	8.0 mg
1,1,1,2-Tetrafluoroethane	18.2 g

The active ingredients were initially weighed in an aluminum can. The metering valve was then placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 26

Ingredients	Quantity (Per aerosol housing)
Terbutaline sulphate	40 mg
Tiotropium bromide	1.8 mg
Fluticasone	8.0 mg
Ethanol	2.73 g
1,1,1,2-Tetrafluoroethane	12.2 g

The active ingredients were initially weighed in an aluminum can, then ethanol was added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 27

Ingredients	Quantity (Per aerosol housing)
Terbutaline sulphate	40 mg
Tiotropium bromide	1.8 mg
Fluticasone	8.0 mg
Ethanol	2.73 g
Lecithin	1.38 mg
1,1,1,2-Tetrafluoroethane	15.83 g

The active ingredients were initially weighed in an aluminum can, then ethanol and lecithin were added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 28

Ingredients	Quantity (Per aerosol housing)
Tiotropium bromide	1.8 mg
Salmeterol	5.81 mg
Fluticasone	20.0 mg
1,1,1,2-Tetrafluoroethane	12.2 g

The active ingredients were initially weighed in an aluminum can. Metering valve was then placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 29

Ingredients	Quantity (Per aerosol housing)
Tiotropium bromide	1.8 mg
Salmeterol	5.81 mg
Fluticasone	20.0 mg
Ethanol (2%)	0.244 g
1,1,1,2-Tetrafluoroethane	12 g

The active ingredients were initially weighed in an aluminum can, then ethanol was added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 30

Ingredients	Quantity (Per aerosol housing)
Tiotropium bromide	1.8 mg
Salmeterol	5.81 mg
Fluticasone	20.0 mg
Ethanol (2%)	0.244 g
Oleic acid (0.02%)	0.003 mg
1,1,1,2-Tetrafluoroethane	12 g

The active ingredients were initially weighed in an aluminum can, then ethanol and the surfactant were added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 31

Ingredients	Quantity (Per aerosol housing)
Formoterol	1 mg
Tiotropium Bromide	1.8 mg
Budesonide	8.0 mg
1,1,1,2-Tetrafluoroethane	12.2 g

The active ingredients were initially weighed in an aluminum can. Metering valve was then placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 32

Ingredients	Quantity (Per aerosol housing)
Formoterol	1 mg
Tiotropium Bromide	1.8 mg
Budesonide	8.0 mg
Ethanol (15%)	1.83 g
1,1,1,2-Tetrafluoroethane	18.2 g

The active ingredients were initially weighed in an aluminum can, then ethanol was added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

Example 33

Ingredients	Quantity (Per aerosol housing)
Formoterol	1.0 mg
Tiotropium Bromide	1.8 mg
Budesonide	8.0 mg
Ethanol	1.83 g
Lecithin (1%)	0.122 mg
1,1,1,2-Tetrafluoroethane	18.2 g

The active ingredients were initially weighed in an aluminum can, then ethanol and the surfactant were added and the solution was sonicated for 5 minutes. The metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA134a was charged through the metering valve.

The following Examples are inhalation powders suitable for DPIs, and were prepared by techniques well known in the art.

Example 34

Ingredients	Quantity (in mg per capsule)
Tiotropium bromide	0.018 mg
Salmeterol	0.050 mg

Ciclesonide	0.1-0.4 mcg
Lactose	q.s.5-25 mg

Example 35

Ingredients	Quantity (in mg per capsule)
Formoterol	0.025-0.4 mg
Ipratropium	0.048 mg
Budesonide	0.1-0.4 mg
Lactose	q.s. 5-25 mg

Example 36

Ingredients	Quantity (in mg per capsule)
Tiotropium Bromide	0.018 mg
Formoterol	0.025-0.4 mg
Ciclesonide	0.1-0.4 mg
Lactose	q.s. 5-25 mg

Example 37

Ingredients	Quantity (in mg per capsule)
Salbutamol sulphate	0.2 mg
Beclomethasone	0.1-0.4 mg
Ipratropium	0.048 mg
Lactose	q.s. 5-25 mg

Example 38

Ingredients	Quantity (in mg per capsule)
Salbutamol sulphate	0.2 mg

Tiotropium bromide	0.018 mg
Budesonide	0.1-0.4 mg
Lactose	q.s. 5-25 mg

Example 39

Ingredients	Quantity (in mg per capsule)
Terbutaline sulphate	0.1-0.2 mg
Tiotropium bromide	0.018 mg
Fluticasone	0.025-0.4 mg
Lactose	q.s. 5-25 mg

The following Examples are for propellant free inhalation solutions, and were prepared by techniques well known in the art.

Example 40

Ingredients	Quantity (%w/v)
Terbutaline sulphate	0.25
Ipratropium bromide	0.025
Fluticasone	0.025-0.1
Polysorbat –80	0.1
Sodium chloride	0.9
Anhydrous citric acid	q.s. to pH 4.5
Water, purified	100 ml

Example 41

Ingredients	Quantity (%w/v)
Ipratropium bromide	0.025

Salbutamol sulphate	0.125
Budesonide	0.05
Polysorbat –80	0.1
Sodium chloride	0.9
Water, purified	100 ml

Example 42

Ingredients	Quantity (%w/v)
Ipratropium bromide	0.025
Salmeterol	0.005
Fluticasone propionate	0.025-0.1
Polysorbat –80	0.1
Sodium chloride	0.9
Water, purified	100 ml

Example 43

Ingredients	Quantity (%w/v)
Ipratropium bromide	0.025
Salmeterol	0.005
Budesonide	0.05
Polysorbat –80	0.1
Sodium chloride	0.9
Water, purified	100 ml

CLAIMS:

1. A pharmaceutical product comprising any one of the following combinations of therapeutic agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more of the therapeutic agents is indicated:

(i) salmeterol, ciclesonide and tiotropium;
(ii) formoterol, budesonide and ipratropium;
(iii) formoterol, ciclesonide and tiotropium;
(iv) formoterol, budesonide and oxitropium;
(v) salbutamol, beclomethasone and ipratropium;
(vi) salbutamol, budesonide and tiotropium;
(vii) terbutaline, fluticasone and tiotropium;
(viii) terbutaline, fluticasone and ipratropium;
(ix) salbutamol, budesonide and ipratropium;
(x) salmeterol, fluticasone and ipratropium;
(xi) salmeterol, budesonide and ipratropium;
(xii) salmeterol, fluticasone and tiotropium; and
(xiii) formoterol, budesonide and tiotropium;

wherein the above therapeutic agents can optionally be present as a pharmaceutically acceptable salt or ester thereof, or in enantiomerically pure form or as a racemic mixture.

2. A pharmaceutical product according to claim 1, which comprises any one of the following combinations of therapeutic agents:

(i) salmeterol, ciclesonide and tiotropium bromide;
(ii) formoterol, budesonide and ipratropium;
(iii) formoterol, ciclesonide and tiotropium bromide;
(iv) formoterol, budesonide and oxitropium;
(v) salbutamol sulphate, beclomethasone and ipratropium;
(vi) salbutamol sulphate, budesonide and tiotropium bromide;
(vii) terbutaline sulphate, fluticasone and tiotropium bromide;
(viii) terbutaline sulphate, fluticasone and ipratropium bromide;

(ix) salbutamol sulphate, budesonide and ipratropium bromide;

(x) salmeterol, fluticasone propionate and ipratropium bromide;

(xi) salmeterol, budesonide and ipratropium bromide;

(xii) salmeterol, fluticasone propionate and tiotropium bromide; and

(xiii) formoterol, budesonide and tiotropium bromide.

3. A pharmaceutical composition comprising any one of the following combinations of therapeutic agents:

(i) salmeterol, ciclesonide and tiotropium;

(ii) formoterol, budesonide and ipratropium;

(iii) formoterol, ciclesonide and tiotropium;

(iv) formoterol, budesonide and oxitropium;

(v) salbutamol, beclomethasone and ipratropium;

(vi) salbutamol, budesonide and tiotropium;

(vii) terbutaline, fluticasone and tiotropium;

(viii) terbutaline, fluticasone and ipratropium;

(ix) salbutamol, budesonide and ipratropium;

(x) salmeterol, fluticasone and ipratropium;

(xi) salmeterol, budesonide and ipratropium;

(xii) salmeterol, fluticasone and tiotropium; and

(xiii) formoterol, budesonide and tiotropium;

wherein the above therapeutic agents can optionally be present as a pharmaceutically acceptable salt or ester thereof, or in enantiomerically pure form or as a racemic mixture, together with a pharmaceutically acceptable carrier or excipient therefor.

4. A composition according to claim 3, which comprises any one of the following combinations of therapeutic agents:

(i) salmeterol, ciclesonide and tiotropium bromide;

(ii) formoterol, budesonide and ipratropium;

(iii) formoterol, ciclesonide and tiotropium bromide;

(iv) formoterol, budesonide and oxitropium;

(v) salbutamol sulphate, beclomethasone and ipratropium;

(vi) salbutamol sulphate, budesonide and tiotropium bromide;
(vii) terbutaline sulphate, fluticasone and tiotropium bromide;
(viii) terbutaline sulphate, fluticasone and ipratropium bromide;
(ix) salbutamol sulphate, budesonide and ipratropium bromide;
(x) salmeterol, fluticasone propionate and ipratropium bromide;
(xi) salmeterol, budesonide and ipratropium bromide;
(xii) salmeterol, fluticasone propionate and tiotropium bromide; and
(xiii) formoterol, budesonide and tiotropium bromide.

5. A composition according to claim 3 or 4, wherein the anti-cholinergic of the composition is present in an amount 0.001wt% to 0.5wt% based on the weight of the total composition.

6. A composition according to any of claims 3 to 5, wherein the β-2 agonist of the composition is present in an amount 0.001wt% to 0.5wt% based on the weight of the total composition.

7. A composition according to any of claims 3 to 6, wherein the steroid of the composition is present in an amount 0.001wt% to 0.5wt% based on the weight of the total composition.

8. A composition according to any of claims 3 to 7, in a form suitable for administration by inhalation.

9. A composition according to claim 8, in the form of an aerosol.

10. A composition according to claim 9, which further comprises a propellant selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, monofluorotrichloromethane and dichlorodifluoromethane, or any mixture of two or more thereof.

11. A composition according to claim 9 or 10, further comprising a co-solvent.

12. A composition according to claim 11, wherein the co-solvent is ethanol.

13. A composition according to any of claims 9 to 12, further comprising a surface-active agent.

14. A composition according to claim 13, wherein the surface-active agent is oleic acid, lecithin, or sorbitol trioleate.

15. A composition according to any of claims 9 to 14, which comprises any one of the following combinations of therapeutic agents:

(i) salmeterol, ciclesonide and tiotropium;
(ii) formoterol, budesonide and ipratropium;
(iii) formoterol, ciclesonide and tiotropium;
(iv) formoterol, budesonide and oxitropium;
(v) salbutamol, beclomethasone and ipratropium;
(vi) salbutamol, budesonide and tiotropium;
(vii) terbutaline, fluticasone and tiotropium;
(viii) salmeterol, fluticasone and tiotropium; and
(ix) formoterol, budesonide and tiotropium;

wherein the above therapeutic agents can optionally be present as a pharmaceutically acceptable salt or ester thereof, or in enantiomerically pure form or as a racemic mixture.

16. A composition according to claim 15, which comprises any one of the following combinations of therapeutic agents:

(i) salmeterol, ciclesonide and tiotropium bromide;
(ii) formoterol, budesonide and ipratropium;
(iii) formoterol, ciclesonide and tiotropium bromide;
(iv) formoterol, budesonide and oxitropium;
(v) salbutamol sulphate, beclomethasone and ipratropium;
(vi) salbutamol sulphate, budesonide and tiotropium bromide;
(vii) terbutaline sulphate, fluticasone and tiotropium bromide;

(viii) salmeterol, fluticasone propionate and tiotropium bromide; and

(ix) formoterol, budesonide and tiotropium bromide.

17. A metered dose inhaler which contains a composition as defined in any of claims 9 to 16.

18. A composition according to claim 8, in the form of an inhalation powder.

19. A composition according to claim 18, which comprises lactose as the excipient.

20. A composition according to claim 18 or 19, which comprises any one of the following combinations of therapeutic agents:

(i) salmeterol, ciclesonide and tiotropium;

(ii) formoterol, budesonide and ipratropium;

(iii) formoterol, ciclesonide and tiotropium;

(iv) salbutamol, beclomethasone and ipratropium;

(v) salbutamol, budesonide and tiotropium;

(vi) terbutaline, fluticasone and tiotropium;

(vii) salmeterol, fluticasone and tiotropium; and

(viii) formoterol, budesonide and tiotropium;

wherein the above therapeutic agents can optionally be present as a pharmaceutically acceptable salt or ester thereof, or in enantiomerically pure form or as a racemic mixture.

21. A composition according to claim 20, which comprises any one of the following combinations of therapeutic agents:

(i) salmeterol, ciclesonide and tiotropium bromide;

(ii) formoterol, budesonide and ipratropium;

(iii) formoterol, ciclesonide and tiotropium bromide;

(iv) salbutamol sulphate, beclomethasone and ipratropium;

(v) salbutamol sulphate, budesonide and tiotropium bromide;

(vi) terbutaline sulphate, fluticasone and tiotropium bromide.

(vii) salmeterol, fluticasone and tiotropium; and

(viii) formoterol, budesonide and tiotropium.

22. A dry powder inhaler which contains a composition as defined in any of claims 18 to 21.

23. A composition according to claim 8, in the form of a propellant free inhalation solution or suspension.

24. A composition according to claim 23, which comprises any one of the following combinations of therapeutic agents:

(i) terbutaline, fluticasone and ipratropium;
(ii) salbutamol, budesonide and ipratropium;
(iii) salmeterol, fluticasone and ipratropium;
(iv) salmeterol, budesonide and ipratropium;
(v) salmeterol, fluticasone and tiotropium; and
(vi) formoterol, budesonide and tiotropium;

wherein the above therapeutic agents can optionally be present as a pharmaceutically acceptable salt or ester thereof, or in enantiomerically pure form or as a racemic mixture.

25. A composition according to claim 24, which comprises any one of the following combinations of therapeutic agents:

(i) terbutaline sulphate, fluticasone and ipratropium bromide;
(ii) salbutamol sulphate, budesonide and ipratropium bromide;
(iii) salmeterol, fluticasone propionate and ipratropium bromide;
(iv) salmeterol, budesonide and ipratropium bromide;
(v) salmeterol, fluticasone propionate and tiotropium bromide; and
(vi) formoterol, budesonide and tiotropium bromide.

26. A composition according to any of claims 23 to 25, in a form suitable for use with a nebuliser.

27. Use of any one of the following combinations in the manufacture of a medicament for

the prophylaxis or treatment of conditions for which administration of one or more of the therapeutic agents is indicated:

(i) salmeterol, ciclesonide and tiotropium;
(ii) formoterol, budesonide and ipratropium;
(iii) formoterol, ciclesonide and tiotropium;
(iv) formoterol, budesonide and oxitropium;
(v) salbutamol, beclomethasone and ipratropium;
(vi) salbutamol, budesonide and tiotropium;
(vii) terbutaline, fluticasone and tiotropium;
(viii) terbutaline, fluticasone and ipratropium;
(ix) salbutamol, budesonide and ipratropium;
(x) salmeterol, fluticasone and ipratropium;
(xi) salmeterol, budesonide and ipratropium;
(xii) salmeterol, fluticasone and tiotropium; and
(xiii) formoterol, budesonide and tiotropium;

wherein the above therapeutic agents can optionally be present as a pharmaceutically acceptable salt or ester thereof, or in enantiomerically pure form or as a racemic mixture.

28. Use according to claim 27, which comprises any one of the following:

(i) salmeterol, ciclesonide and tiotropium bromide;
(ii) formoterol, budesonide and ipratropium;
(iii) formoterol, ciclesonide and tiotropium bromide;
(iv) formoterol, budesonide and oxitropium;
(v) salbutamol sulphate, beclomethasone and ipratropium;
(vi) salbutamol sulphate, budesonide and tiotropium bromide;
(vii) terbutaline sulphate, fluticasone and tiotropium bromide;
(viii) terbutaline sulphate, fluticasone and ipratropium bromide;
(ix) salbutamol sulphate, budesonide and ipratropium bromide;
(x) salmeterol, fluticasone propionate and ipratropium bromide;
(xi) salmeterol, budesonide and ipratropium bromide;
(xii) salmeterol, fluticasone propionate and tiotropium bromide; and
(xiii) formoterol, budesonide and tiotropium bromide.

29. Use according to claim 27 or 28, for the manufacture of a medicament for the treatment of inflammatory or respiratory tract diseases, by simultaneous or successive administration.

30. Use according to claim 29, for the manufacture of a medicament for the treatment of asthma and/or chronic obstructive pulmonary disease (COPD), by simultaneous or successive administration.

31. A method for the prophylaxis or treatment of inflammatory or respiratory tract diseases, said method comprising administering either sequentially or simultaneously, to a patient in need thereof, a therapeutically effective amount of any one of the following combinations:

(i) salmeterol, ciclesonide and tiotropium;
(ii) formoterol, budesonide and ipratropium;
(iii) formoterol, ciclesonide and tiotropium;
(iv) formoterol, budesonide and oxitropium;
(v) salbutamol, beclomethasone and ipratropium;
(vi) salbutamol, budesonide and tiotropium;
(vii) terbutaline, fluticasone and tiotropium;
(viii) terbutaline, fluticasone and ipratropium;
(ix) salbutamol, budesonide and ipratropium;
(x) salmeterol, fluticasone and ipratropium;
(xi) salmeterol, budesonide and ipratropium;
(xii) salmeterol, fluticasone and tiotropium; and
(xiii) formoterol, budesonide and tiotropium;

wherein the above therapeutic agents can optionally be present as a pharmaceutically acceptable salt or ester thereof, or in enantiomerically pure form or as a racemic mixture.

32. A method according to claim 31, which comprises administering either sequentially or simultaneously, to a patient in need thereof, a therapeutically effective amount of any one of

the following combinations:

(i) salmeterol, ciclesonide and tiotropium bromide;
(ii) formoterol, budesonide and ipratropium;
(iii) formoterol, ciclesonide and tiotropium bromide;
(iv) formoterol, budesonide and oxitropium;
(v) salbutamol sulphate, beclomethasone and ipratropium;
(vi) salbutamol sulphate, budesonide and tiotropium bromide;
(vii) terbutaline sulphate, fluticasone and tiotropium bromide;
(viii) terbutaline sulphate, fluticasone and ipratropium bromide;
(ix) salbutamol sulphate, budesonide and ipratropium bromide;
(x) salmeterol, fluticasone propionate and ipratropium bromide;
(xi) salmeterol, budesonide and ipratropium bromide;
(xii) salmeterol, fluticasone propionate and tiotropium bromide; and
(xiii) formoterol, budesonide and tiotropium bromide.

33. A method according to claim 31 or 32, for the treatment of asthma and / or chronic obstructive pulmonary disease (COPD), by simultaneous or successive administration.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/03751

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61K9/72 A61P11/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 423 298 B2 (D.P.MCNAMARA, G.A.DESTEFANO) 23 July 2002 (2002-07-23) claims 1,4,5,14,15,17,20 column 1, line 46-53 column 2, line 33-47 column 3, line 16-28 ---	1-4, 8-16, 27-33
X	M.MIRAVITLLES E.A.: "Treatment and quality of life in patients with chronic obstructive pulmonary disease" QUALITY OF LIFE RESEARCH, vol. 11, no. 4, 2002, pages 329-338, XP008018999 page 329 page 331, column 1 page 332 --- -/--	1,3,8, 27, 29-31,33

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2003	07/11/2003

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/03751

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 07672 A (AEROPHARM TECHNOLOGY) 31 January 2002 (2002-01-31) claims 1,2,4-6,23-25 page 4, line 11-28	1-4, 8-12, 15-17, 27-33
X	R.K.GUPTA, S.K.CHHABRA: "An evaluation of salmeterol in the treatment of chronic obstructive pulmonary diseases" THE INDIAN JOURNAL OF CHEST DISEASES & ALLIED SCIENCES, vol. 44, no. 3, 2002, pages 165-172, XP008018997 page 165 page 166, column 2 page 170 page 171, column 1	1-4,8, 27-33
P,X	WO 03 000241 A (BOEHRINGER INGELHEIM PHARMA) 3 January 2003 (2003-01-03) claims 1-38	1-33

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter[illegible]al application No.
PCT/GB 03/03751

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 31-33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Internat pplication No
PCT/GB 03/03751

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